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TITLE: Instructive Biologic Scaffold for Functional Tissue Regeneration Following Trauma to the Extremities

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14. ABSTRACT

Our hypothesis is that subjects who receive the SIS-ECM scaffold material will have significant new muscle growth and improvements in strength in the treated extremity. The proposed prospective, non-randomized, two-armed study in forty (40) subjects will establish the safety and effectiveness of a regenerative scaffold for the restoration of functional musculotendinous tissue, including the restoration of blood supply and innervation. Cohort 1 will include 20 subjects with upper extremity flexor and extensor traumatic, postoperative, or other avulsive VML. Cohort 2 will include 20 subjects with open femur fractures or soft tissue injury to the thigh resulting in VML. The primary endpoint will be changes in graft site muscle volume compared to baseline at 6 and 12 months as determined by imaging.

15. SUBJECT TERMS
Regenerative Medicine; Extracellular Matrix; Volumetric Muscle Loss

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Table of Contents

1. INTRODUCTION:

The purpose of this investigation was to evaluate the effectiveness of a regenerative biologic scaffold, Biodesign® 6-layer Plastic Surgery Matrix [Cook Biotech]; Premarket Notification Trade/Device Name: SIS Plastic Surgery Matrix, derived from small intestinal submucosa extracellular matrix (SIS-ECM), for the restoration of functional musculotendinous tissue in participants with an acute or subacute volumetric muscle loss (VML) injury. The proposed research was a prospective, multi-center, non-randomized, single-armed, two-cohort clinical trial with a targeted population of forty (40) evaluable subjects. Cohort 1 will include 20 subjects with upper extremity traumatic, postoperative, or other avulsive VML injury. Cohort 2 will include 20 subjects with lower extremity traumatic, postoperative, or other avulsive VML injury. This study was proposed to be conducted at 2 study sites: Walter Reed National Military Medical Center (WRNMMC) and the R Adams Cowley Shock Trauma Center (STC) at the University of Maryland Medical Center. Study participants were planned to be enrolled and followed for a period of 1 year (12 months). This study had the intention to evaluate the effectiveness of Biodesign®, a 6-layer regenerative biologic scaffold derived from small intestinal submucosa extracellular matrix (SIS-ECM), for the restoration of functional musculotendinous tissue in forty (40) participants, both male and female, with an acute or subacute volumetric muscle loss (VML) defects in their upper or lower extremities. The targeted subject population consist of injured service members or civilian victims of trauma. All subjects enrolled were to receive the SIS-ECM scaffold, trimmed to fit the defect, and were to serve as their own control. Only one segmental muscle defect was to be treated in each subject, and each subject may have received multiple SIS-ECM grafts at the injury site. Enrolled participants were to be assigned to 1 of 2 Cohort groups. Cohort 1 were to include 20 subjects with upper extremity traumatic, postoperative, or other avulsive VML injury. Cohort 2 was to include 20 subjects with lower extremity traumatic, postoperative, or other avulsive VML injury.

2. KEYWORDS: Regenerative Medicine; Extracellular Matrix; Volumetric Muscle Loss

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Our hypothesis is that subjects who receive the SIS-ECM scaffold material will have significant new muscle growth and improvements in strength in the treated extremity. The proposed prospective, non-randomized, two-armed study in forty (40) subjects will establish the safety and effectiveness of a regenerative scaffold for the restoration of functional musculotendinous tissue, including the restoration of blood supply and innervation. Cohort 1 will include 20 subjects with upper extremity flexor and extensor traumatic, postoperative, or other avulsive VML. Cohort 2 will include 20 subjects with open femur fractures or soft tissue injury to the thigh resulting in VML. The primary endpoint will be changes in graft site muscle volume compared to baseline at 6 and 12 months as determined by imaging. Secondary endpoints will include histopathological characterization of the muscle healing response at the graft site, clinician and subject evaluation of cosmesis, and comparison of complication rates to clinical site historical standard of care.

What was accomplished under these goals?

Specific Aim 1: To induce the *de novo* formation of at least 25% of the missing muscle tissue using an inductive ECM scaffold. This tissue will be morphologically and structurally identical to native skeletal muscle tissue.

Briefly, Cook BioDesign's Plastic Surgery Matrix® device will be implanted surgically. Change in muscle volume from baseline at device implantation as determined by MRI or CT will be assessed. Biopsied tissue will be fixed and the tissue specimens will be subjected to a battery of immunohistochemical, immunolabeling, and traditional histochemical stains for the identification of cell phenotype, extracellular

matrix characterization, and histomorphometric analysis. The main endpoint of this study was to determine the percentage of volume restored at the surgical site.

Task 1: IRB and Facility Approvals (months 1-4)
- 1a. IRB Approval (months 1-4)
  - Facility: Walter Reed National Military Medical Center (WRNMMC)
- 1b. IRB Approval (months 1-4)
  - Facility: Maryland Shock Trauma (MST)
- 1c. Approval by USAMRMC Office of Research Protections (months 4-5)

As required prior to IRB submission, the WRNMMC protocol was submitted to the departmental Scientific Review Committee (SRC) for review and received back with minimal questions and edits. Kick-off meetings via conference call were conducted on 16 September 2014 with WRNMMC personnel and on 30 October 2014, including current PI, Mr. Janis, and transitioning PI, CDR Fleming, to discuss study roles and responsibilities. Another meeting was conducted on 13 November 2014 between WRNMMC study personnel with the addition of WRNMMC personnel Dr. Dearth and Ms. Pruziner to clarify roles. Additional meetings were conducted on 04 February 2015, 19 February 2015, 12 March 2015, 2 April 2015, 04 June 2015, 11 June 2015, 23 June 2015, 29 October 2015 with WRNMMC study personnel to discuss and clarify study protocol specifics and progress. Conference call meetings were conducted on 04 March 2015, 02 September 2015, 16 September 2015, 30 September 2015 between WRNMMC and MST, including WRNMMC PI CDR Fleming and MST PI Dr. Sciadini, to discuss study protocol and site coordination specifics. An in-person investigators' meeting between WRNMMC and MST was conducted on 27 August 2015, including WRNMMC transitioning PI, LTC Nesti, MST PI Dr. Sciadini, WRNMMC investigator Dr. Dearth, and WRNMMC and MST study coordinators, Ms. Lee and Ms. Ordonio to discuss changes in study personnel and progress. Another in-person investigators' meeting between WRNMMC and MST was conducted on 23 September 2015 at MST with Dr. Dearth and Ms. Pruziner presenting and discussing study protocol with MST investigators. A conference call meeting was conducted on 05 August 2015 with the addition of STATKING personnel to clarify roles and responsibilities. In-person meetings to discuss CRFs were conducted on 04 September 2015 with WRNMMC & MST study personnel and on 21 September 2015 with WRNMMC study personnel.

Task 2: Patient Enrollment (months 5-23)
- 2a. Patient Enrollment (months 5-23)
  - Facility: Walter Reed National Military Medical Center
- 2b. Patient Enrollment (months 5-23)
  - Facility: Maryland Shock Trauma
- # Clinical Patients: 40

Patient Enrollment did not occur.

Task 3: Patient Follow Up (months 8-31)
- 3a. CT Guided Biopsy (months 8-31)
  - Facility: Walter Reed National Military Medical Center
- 3b. MRI, MRI Guided Biopsy (months 8-31)
  - Facility: Maryland Shock Trauma
- # Clinical Patients: 40

Patient Follow Up did not occur.

Task 4: Histology/Pathology (months 8-35)
- 4a. Histology (months 8-35)

Facility: WRNMMC
4b. Pathology (months 8-35)
Tissue Samples: 80

Histology and Pathology did not occur.

Task 5: Final Report (months 35-37)
5a. Review of Data and Generation of Final Report (months 35-37)
Facility: WRNMMC
Pathology reports, functional test scores, and imaging data were to be assessed by Dr. Leon Nesti and study personnel. These data were to be tabulated and forwarded to the biostatistician for statistical analysis as described in the statistical plan. A final report incorporating these data will be prepared, reviewed and accepted by the PIs at WRNMMC and Maryland Shock Trauma.

Specific Aim 2: To restore at least 25% of the function of the involved muscle group through the use of an inductive ECM scaffold material.

Briefly, functional recovery in the injured extremity was to be compared at 1, 4, 8, and 12 months. At 12 months, function of the injured extremity will be compared to the contralateral limb, if present. The main endpoint of this study was to determine the percentage of function restored to the surgical site.

Task 6: Patient Follow Up (months 8-31)
6a. Functional and Physician Assessment (months 8-31)
Facility: Walter Reed National Military Medical Center
6b. Functional and Physician Assessment (months 8-31)
Facility: Maryland Shock Trauma
Clinical Patients: 40

Patient Follow Up did not occur

Task 7: Final Report (months 31-47)
7a. Review of Data and Generation of Final Report (months 31-47)
Facility: WRNMMC
Pathology reports, functional test scores, and imaging data will be assessed by the research team at WRNMMC. These data will be tabulated and forwarded to the biostatistician for statistical analysis as described in the statistical plan. A final report incorporating these data will be prepared, reviewed, and accepted by investigators.

What opportunities for training and professional development has the project provided?

Training and professional development activities occurred between current and former investigators and collaborators at the Military Health System Research Symposium (MHSRS), Ft Lauderdale, Florida in August 2015 and also at the Tissue Engineering and Regenerative Medicine International Society (TERMIS) World Conference, Boston, Massachusetts in September 2015.

How were the results disseminated to communities of interest?

Nothing to Report

What do you plan to do during the next reporting period to accomplish the goals?

Nothing to report

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to Report

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change:

The project has been terminated.

Actual or anticipated problems or delays and actions or plans to resolve them

Nothing to Report

Changes that had a significant impact on expenditures

Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to Report

6. PRODUCTS:

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	CAPT Mark Fleming, CAPT, MC, USN
Project Role:	Principal Investigator (PI) / Site Principal Investigator at WRNMMC
Nearest person month worked:	12 months
Contribution to Project:	Dr. Fleming is an orthopedic trauma surgeon, was the site

Principal Investigator (PI) at WRNMMC and then transitioned to take over the role of study PI from Abram Janis.

Name: LTC Leon Nesti, MD, PhD
LTC, MC, USA
Project Role: Principal Investigator (PI) / Site Principal Investigator at WRNMMC, Associate Professor, Uniformed Services University
Nearest person month worked: 2 months
Contribution to Project: Dr. Nesti is a hand and upper extremity orthopedic reconstructive surgeon at WRNMMC who has transitioned to take over the role of study PI from Dr. Fleming, and has extensive research experience.

Name: Marcus Sciadini, MD
Project Role: Site Principal Investigator at MST
Nearest person month worked: 12 months
Contribution to Project: Dr. Sciadini is an orthopedic trauma surgeon and the site Principal Investigator (PI) at MST, provided clinical expertise and input on study protocol and design.

Name: Barry Martin, COL, MC, USA
Project Role: Associate Investigator, Plastic & Reconstructive Surgeon
Nearest person month worked: 9 months
Contribution to Project: Dr. Martin, is a reconstructive plastic surgeon, has provided expertise in soft tissue reconstruction, clinical applications of regenerative medicine, and provided input on study protocol and design.

Name: Ian Valerio, MD, MS, MBA, FACS, CDR, MC, USNR
Project Role: Collaborator / Consultant
Nearest person month worked: 6 months
Contribution to Project: Dr. Valerio, is a reconstructive plastic surgeon, former Co-Investigator (Co-I) at WRNMMC, and has provided expertise in soft tissue reconstruction, clinical applications of regenerative medicine, and provided input on study protocol and design.

Name: Christopher Dearth, PhD
Project Role: Associate Investigator & Subject Matter Expert at WRNMMC
Facility Research Director, DoD-VA Extremity Trauma & Amputation Center of Excellence
Nearest person month worked: 11 months
Contribution to Project: Dr. Dearth is a Scientist Subject Matter Expert at WRNMMC, facility research director, has expertise in muscle regenerative research, provided input on study protocol and design, and will assist with processing biopsies, histological evaluations and publications.

Name: Alison Pruziner, PT, DPT, ATC
Project Role: Associate Investigator & Research Physical Therapist at WRNMMC, DoD-VA Extremity Trauma & Amputation Center of Excellence

Nearest person month worked:	11 months
Contribution to Project:	Alison is a research physical therapist at WRNMMC, has expertise in physical therapy research, provided input on study protocol and design, and will assist with subject visits, functional assessments, and training PT personnel.
Name:	Shannon M. Lynch, PT, DPT, OCS LTC, SP
Project Role:	Associate Investigator, Physical Therapist & Service Chief at WRNMMC
Nearest person month worked:	12 months
Contribution to Project:	LTC Lynch is a physical therapist and service chief at WRNMMC, has expertise in physical therapy research, provided input on study protocol and design, and will assist with subject visits, functional assessments, and training PT personnel.
Name:	Michael Stidham, PT
Project Role:	Associate Investigator & Physical Therapist at WRNMMC
Nearest person month worked:	5 months
Contribution to Project:	Michael is a physical therapist at WRNMMC, has experience in physical therapy research, provided input on study protocol and design, and will assist with subject visits and functional assessments.
Name:	Nancy Lee
Project Role:	Research Associate / Coordinator at WRNMMC
Nearest person month worked:	12 months
Contribution to Project:	Nancy Lee has performed work as a research coordinator at WRNMMC, facilitated communications between investigators, assisted with the protocol, CRFs, notes and reports.
Name:	Katherine Ordonio
Project Role:	Clinical Research Specialist / Coordinator at MST
Nearest person month worked:	2 months
Contribution to Project:	Katherine Ordonio has performed work as a research coordinator at MST, facilitated communications between investigators, assisted with the protocol and CRFs.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

No.

What other organizations were involved as partners?

Organization Name: R Adams Cowley Shock Trauma Center (STC), University of Maryland Medical Center
Location of Organization: 22 S. Greene Street, Baltimore, MD 21201
Partner's contribution to the project: Facilities and collaboration (i.e. partner's staff work with project staff on the project);

Organization Name: STATKING Clinical Services
Location of Organization: 759 Wessel Drive, Fairfield, OH 45014
Partner's contribution to the project: Clinical Monitoring & Data Management

8. SPECIAL REPORTING REQUIREMENTS: Nothing to report

9. APPENDICES: Nothing to report